Dietary Supplements: Safety and Regulatory Concerns

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Botanicals & other natural products: What kind of product?

- Main Entry: **bound·ary**
  Pronunciation: 'baun-d(&-)rE
  Function: *noun*
  Inflected Form(s): *plural* **-aries**
  Date: 1626
  : something (as a line, point, or plane) that indicates or fixes a limit or extent
- Food vs. drug

What Is a Food Today?
Food Terminology 101

Conventional foods

Farmaceutical

Dietary supplements

Functional foods

Infant formulas

Medical food

Unconventional foods

Foods for special dietary use

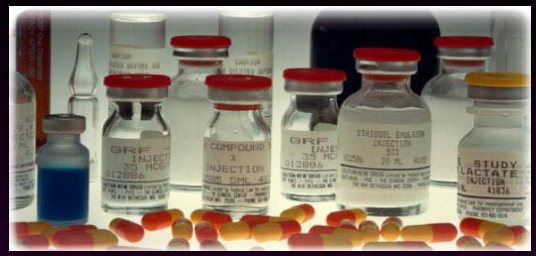
Nutriceuticals

Exempt infant formulas

Nutritional supplements

Special nutritionals

Pharmafoods



Foods ⟷ *Drugs*

Conventional foods

Dietary supplements

Medical foods

Infant formulas

R_x

Food for special dietary use

OTC

Biologics

Exempt infant formulas

Devices

Functional foods

Nutriceuticals

Regulatory classification of product matters because.....

- Different regulatory requirements
- Different substantiation
- Different safety considerations

How are botanicals regulated by FDA?

- It depends on:
  - how the product is marketed by the manufacturer

Product claims determines regulatory class

- Drug: diagnosis, cure, mitigation, treatment, or prevention of disease
  - Disease claim = drug
    - “damage to an organ, part, structure, or system of the body such that it does not function properly…or a state of health leading to such dysfunctioning…”

D ietary

S upplement

H ealth and

E ducation

A ct

Dietary Supplements: DSHEA Definition

- Intended to supplement the diet
- Contains one or more of the following dietary ingredients:
  - Vitamin, mineral, amino acid
  - Herb or other botanical (not tobacco)
  - "dietary substance" for use by man to supplement the diet by increasing the total dietary intake
  - Concentrate, metabolite, constituent, extract, or combination of any of the above

Dietary Supplements under DSHEA

- A product that is:
  - Ingested in tablet, capsule, liquid, powder, gelcap, softgel
  - Not represented as conventional food
  - Not represented as sole item of meal
  - Not represented as a total diet
  - Labeled as a dietary supplement

Dietary Supplements under DSHEA

Exclusions: Does not include articles that are:

- Approved new drugs, antibiotics, or biologics
- Authorized investigational new drug, antibiotic, or biologic

➔ *UNLESS* first marketed as a dietary supplement

➔ for INDs:

- authorized
- "substantial clinical studies" initiated
- "existence…has been made public"

Dietary Supplements Post- DSHEA

- No pre-market registration, review, or approval by FDA
- Exempt from food additive provisions
- "Optional" GMP regulations
- FDA bares the burden of proving a dietary supplement is unsafe

Summary: Current Safety Standards

Category	Standard	Determination
Conventional Food	Reasonable certainty of no harm	Manufacturer
Food additive	Reasonable certainty of no harm	FDA
GRAS ingredient	Reasonable certainty of no harm	Manufacturer
Old DS ingredient	No significant or unreasonable risk	Manufacturer
New DS ingredient	Sufficient evidence of no significant / unreasonable risk	Manufacturer
Drug	Safe and effective	FDA

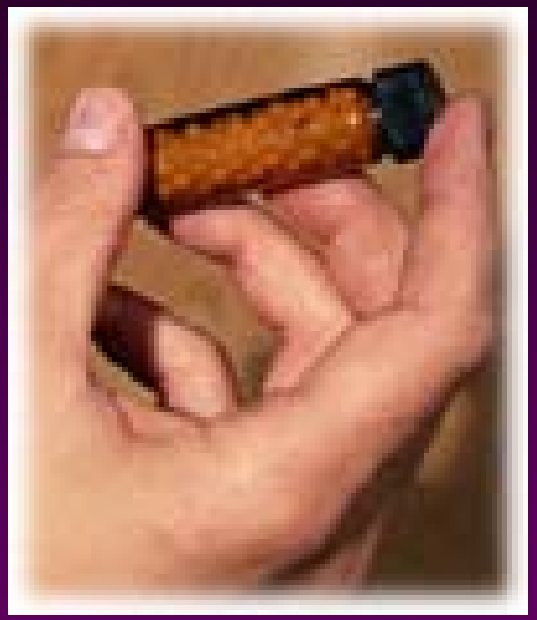
FDA's efforts on dietary supplements are focused on the postmarketing period

- Adverse event monitoring
- Other:
  - Product sampling
  - Scientific literature
  - Other sources
- Compliance and enforcement

Labeling

- In addition to setting product standards, FDA regulates the labeling of products under its jurisdiction.
  - Information must be rigorously truthful, well documented, and not misleading.

Good manufacturing practices

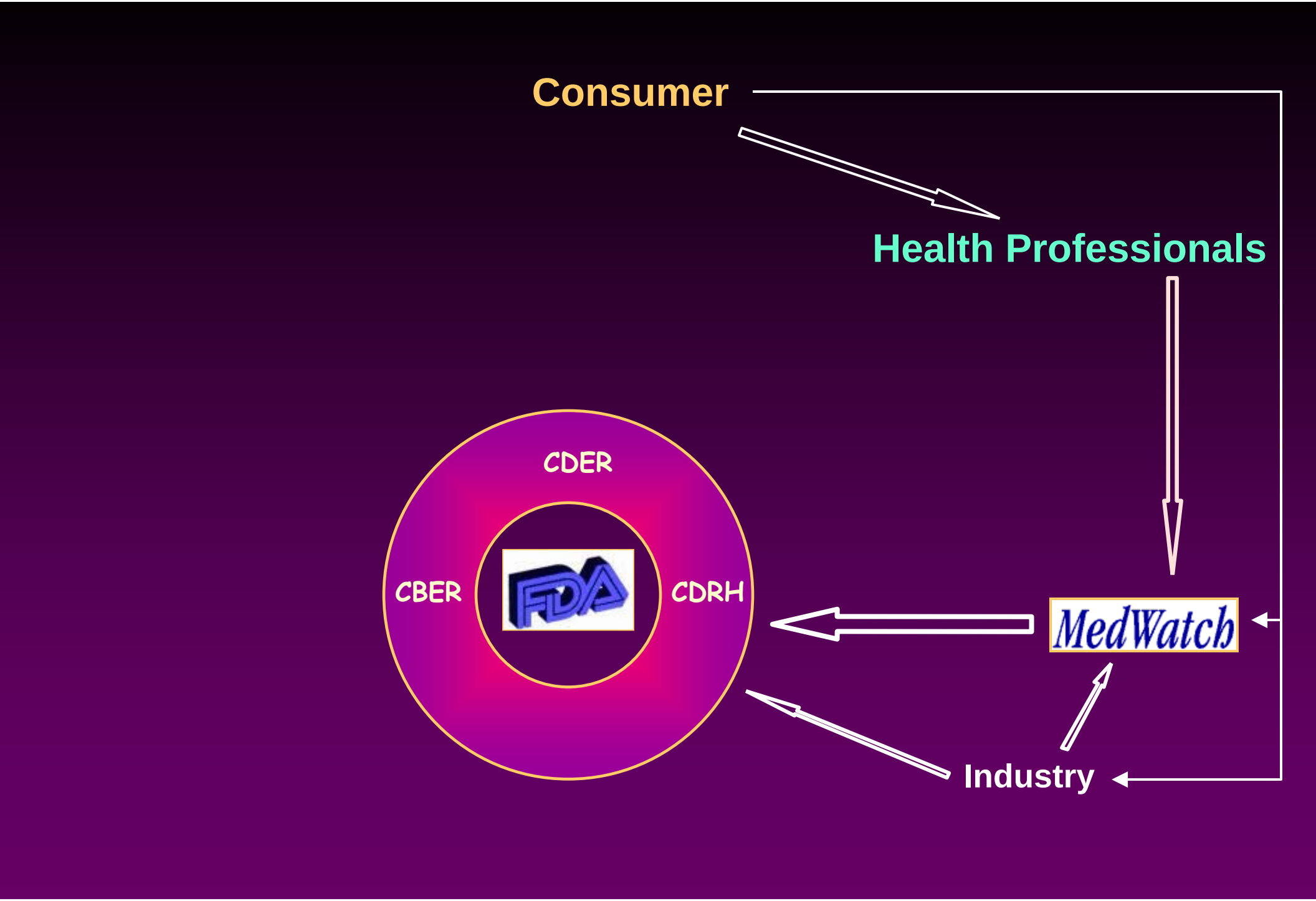


- Purpose: to make sure that products are manufactured to the same high standards
- Specific type depends upon product classification
- Periodic inspection of firm by ORA to evaluate compliance with GMPs.

Adverse event reporting

- Many systems in different FDA centers
- No central system based on type of ingredients
  - Adverse event report goes ultimately to Center with regulatory responsibility for the particular product

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM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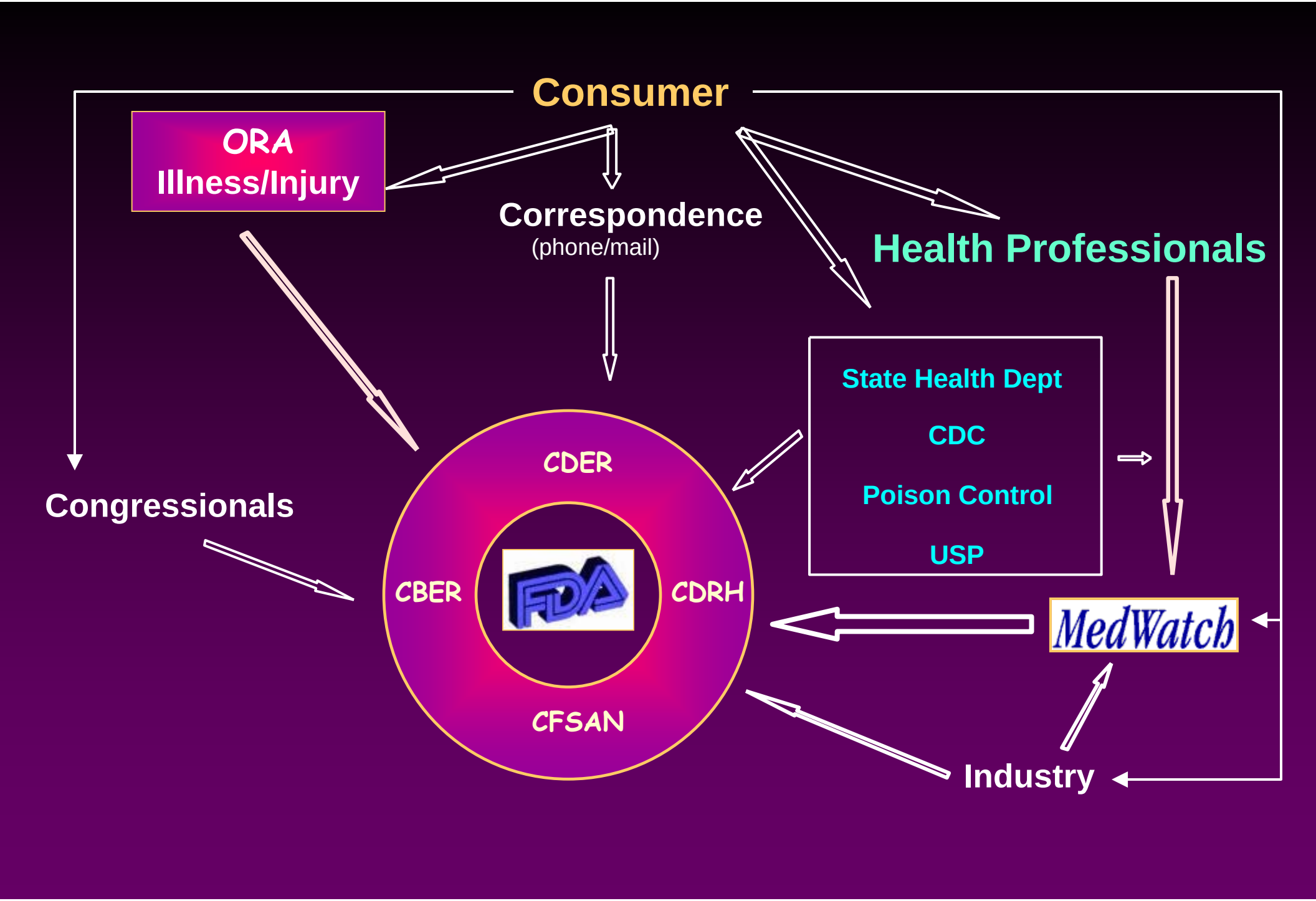
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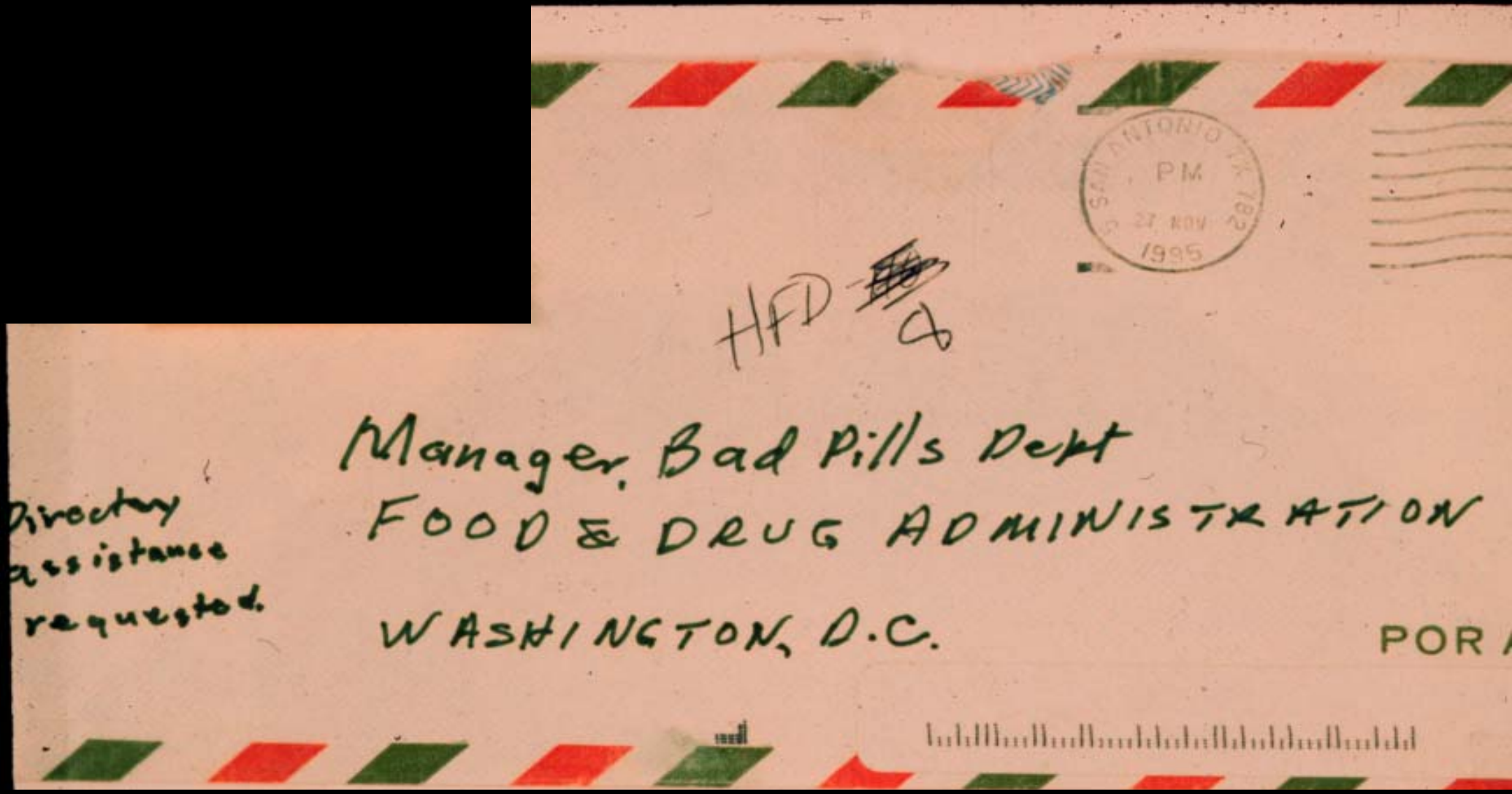
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Postmarketing Safety Considerations

- Characteristics of adverse events
  - nature, severity, consequences
- Population affected
  - vulnerable groups

Postmarketing Safety Considerations

	Medicinal Products & Special Nutritionals	**Conventional Foods**
AE Categories:	high potential many different types	limited, e.g. infections, food sensitivities
AE Etiologies:	multiple, often unknown	microbial & allergy or sensitivity
AE Duration:	often chronic	acute, self-limited
AE Evaluation:	extensive follow up & evaluation	usually limited

"Natural" Products:

- Hemlock
- Digitalis
- Taxol
- Arsenic, lead, mercury
- Cobra venom
- Bacteria, viruses
- Insects, fungi

It's all "natural"….!

"People can be induced to swallow anything, provided it is sufficiently seasoned with praise."

Moliere (17th Century French playwright)

"Natural" Products

- Every product with known pharmacological activity has shown adverse effects in some individuals when studied appropriately.

Why historical use can not be relied on to provide evidence of safety:

- No documented systems to collect and evaluate adverse effects associated with product use
  - If you don't take a temperature, you will not find a fever!

Why historical use can not be relied on to provide evidence of safety:

- Different products, populations and use patterns today compared to historical use

Comparison of historical use of botanicals to current use as dietary supplements

- Using Ephedra containing products as an example

Product:	***Historical Use***	***Current Use in the USA***
Category:	Medicine	Dietary supplement
Selection:	HCP prescribed	Consumer selected
Use:	Respiratory disorders	Weight loss, energy, other
Formulation:	HCP selected, defined herbal combinations	manufacturer selected, combinations of ingredients not used traditionally
Duration of use:	Short term	Undefined, can be prolonged

Common Misperceptions about Dietary Supplement/Other Natural Products:

- "Natural" = safe
- "Historical use" = safe
- FDA approves/reviews these products prior to marketing
- If one is good, more must be better

Botanical and Other "Natural" Ingredients with Safety Concerns:

Adverse Effects	***Product / Ingredient***
CVS	*Ephedra spp.* (ma huang)
	St. John's wort
CNS	*Ephedra spp.,*
	Germander *(Teucrium chamaedrys)*
	Valerian
	GBL/GHB

Botanical and Other "Natural" Ingredients with Safety Concerns:

Adverse Effects	***Product / Ingredient***
Hepatotoxicity	Chaparral *(Larrea dentata),* PA *(Symphytum, Senecio spp),* Germander *(Teucrium chamaedrys)* Kava kava Anthraquinone laxatives (senna, cascara, aloe) Vitamin A

Botanical and Other "Natural" Ingredients with Safety Concerns:

Adverse Effects	***Product / Ingredient***
Nephrotoxicity	Germanium
	Aristolochia
Myopathy	L-Tryptophan/ 5-HTP
	Niacin
Coagulapathy	*Ginkgo biloba*
	Glucosamine/ chrondoitin SO4

Safety Considerations

- Product is directly harmful

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- Product is directly harmful
- Product is adulterated or contaminated

Safety Concerns Because of Contaminants or Adulterants

- Pesticides
- Microbial contamination
- Molds, mycotoxins
- Filth
- Heavy metals:
  - Bee products contaminated with lead
- Drugs, chemicals
  - Black pearls, jin bu huan other “patent” medicines
- Misidentified or substituted ingredients
  - Plaintain contaminated with digitalis

Safety Considerations

- Product is directly harmful
- Product is adulterated or contaminated
- Product - product or other co-factor interactions occur

Product Interactions

- Increased anticoagulant effects
  - NSAIDS or warfarin with white willow, garlic, ginger, feverfew, ginkgo, or vitamin E
- Increased cardiovascular and nervous system stimulation
  - Cardiac drugs, MAOI, caffeine, or cough/cold/other products with ephedra, kola, guarana, khat, or yohimbe
  - MAOI, SSRI, or ß-sympathomimetics with St. John's wort

Product Interactions

- Increased nervous depression
  - barbiturates with valerian
  - benzodiazepines with kava

Safety Concerns due to Co-factor Interactions

- Pharmacogenetics
- Immunogenetics
- Age, gender or health condition

Safety Considerations

- Product is directly harmful
- Product is adulterated or contaminated
- Product - product or other co-factor interactions occur
- Product is substituted for a known effective therapy

Ongoing Challenges in the Dietary Supplement Arena

- Ingredient and product standardization
- Ascertainment of ingredient / product effects
- Establishment of appropriate conditions of use
- Monitoring safety of products

Help FDA in its safety mission: report adverse events:

U.S. Food and Drug Administration

MedWatch: *The FDA Safety Information and Adverse Event Reporting Program*

- Mail: via postage-paid MedWatch form
- Phone: 1-800-FDA-1088
- Fax: 1-800-FDA-1078
- Internet: http://www.fda.gov.medwatch

Information Sources:

- 
  - http://wwwfda.gov.fda
  - http://www.cfsan.fda.gov/~dms/supplmnt.html
- NIH 
  
  - http://nccam.nih.gov/
  - http://www.nlm.nih.gov/nccam/camonpubmed.html
  - http://dietary-supplements.info.nih.gov/